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Original Article

Taxane-based Induction Chemotherapy Plus Concurrent Chemoradiotherapy in Nasopharyngeal Carcinoma: Prospective Results from a Non-endemic Cohort

S. Ghosh-Laskar [*], A. Pilar [*], K. Prabhash [†], A. Joshi [†], J.P. Agarwal [*], T. Gupta [*], A. Budrukkar [*], V. Murthy [*], M. Swain [*], V. Noronha [†], V.M. Patil [†], P. Pai [‡], D. Nair [‡], D.A. Chaukar [‡], S. Thiagarajan [‡], G. Pantvaidya [‡], A. Deshmukh [‡], P. Chaturvedi [‡], S. Nair [‡], A. D'Cruz [‡]

[*] *Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India*
[†] *Department of Medical Oncology, Tata Memorial Hospital, Mumbai, India*
[‡] *Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, India*

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Abstract

Aims: To report the outcomes of induction chemotherapy (ICT) followed by chemoradiotherapy (CTRT) for a large cohort of locoregionally advanced nasopharyngeal cancer (LA-NPC) from a non-endemic region.
Materials and methods: Between January 2008 and July 2015, 201 patients with histologically proven, non-metastatic NPC were treated with ICT followed by CTRT at our institute. All the patients received two to three cycles of a taxane-based ICT regimen. Radiotherapy was delivered using an intensity-modulated radiotherapy (IMRT) technique in all patients.
Results: After a median follow-up of 37 months (range: 7–110 months), the 3-year disease-free survival (DFS), locoregional relapse-free survival (LRFS), distant metastasis-free survival (DMFS) and overall survival of the entire cohort was 72, 85, 83 and 87.4%, respectively. On multivariate analysis, histology was an independent predictor of DFS, LRFS and overall survival, with keratinising squamous cell carcinoma histologies predicting a worse outcome. The nodal stage was an independent predictor of DFS, DMFS and overall survival. Age, gender, ethnicity, tumour stage and response to ICT did not significantly affect any of the outcomes. Grade 2 or worse subcutaneous fibrosis was seen in 19% of patients at last follow-up and grade 2 or worse xerostomia was seen in 24% of patients. Thirty-nine per cent of patients developed clinical hypothyroidism at last follow-up.
Conclusion: ICT followed by concurrent CTRT in the IMRT era provides excellent locoregional control, distant control and overall survival rates in patients with LA-NPC. However, distant failure continues to be a problem and may require further systemic intensification.

Key words: Induction chemotherapy; intensity-modulated radiotherapy; nasopharyngeal cancer; outcomes

Introduction

Nasopharyngeal cancer (NPC) is a radio- and chemosensitive malignancy and, thus, chemoradiotherapy (CTRT) forms the mainstay of treatment of NPC. Despite this, the optimal sequencing of chemotherapy with radiotherapy for locoregionally advanced NPC (LA-NPC) remains uncertain.

The Intergroup 0099 study [1] and many other phase III trials [2–5] established concurrent CTRT followed by adjuvant chemotherapy (ACT) as the standard of care in LA-NPC. However, given the poor compliance (60%) to ACT after CTRT, the actual benefit with ACT remains a point of controversy. The consensus to date has been that CTRT provides the maximum benefit in terms of local control, locoregional relapse-free survival (LRFS) and overall survival [6]; the role of additional chemotherapy remains unanswered. There has also been an improvement in radiotherapy techniques for NPC since the Intergroup 0099 results and with the use of intensity-modulated radiotherapy (IMRT) in the modern

Author for correspondence: S.Ghosh-Laskar, Department of Radiation Oncology, Tata Memorial Hospital, Dr. Ernest Borges Marg, Parel, Mumbai, 400012, India. Tel: +91-22-24177162; Fax: +91-22-24146937.
E-mail address: sarbanilaskar@gmail.com (S. Ghosh-Laskar).

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era, locoregional control of 85–90% can be achieved with CTRT [7–9].

Despite the excellent LRFS with the use of CTRT, distant metastases remain the predominant problem in LA-NPC – almost 22% at 3 years [10], emphasising the need for further intensification of systemic treatment. However, given the poor compliance to ACT, many have reason to believe that ACT is probably not the best method to intensify systemic treatment and thus induction chemotherapy (ICT) has re-emerged as an attractive option for treatment intensification.

Recently, a large phase III trial [11] of ICT followed by CTRT versus CTRT alone showed a disease-free survival (DFS) and overall survival benefit in the ICT arm due to a significant reduction in distant metastases rate. However, most of the published literature on ICT reports results of treatment from the endemic regions where the tumour biology may be different from non-endemic areas. Herein we report our experience with ICT followed by CTRT for a large cohort of LA-NPC from a non-endemic region treated in the modern IMRT era.

Materials and Methods

Patient and Tumour Characteristics

Since the publication of Intergroup 0099 [1] in 1998, LA-NPC patients at our institute have typically been treated with CTRT alone or ICT followed by CTRT. The decision to replace the ACT part of the Intergroup 0099 regimen with ICT was made due to the better compliance in the ICT protocol. Also, it was logistically more appealing for a busy department to be able to accommodate all patients for IMRT and reduce rates of re-planning on CTRT. Taxane-based chemotherapy was introduced into the induction regimen for LA-NPC in 2007 after the demonstration of its efficacy in improving outcomes in other head and neck cancers [12,13]. IMRT was routinely used in clinical practice in December 2007 and since then all consecutive patients with LA-NPC have been treated with ICT followed by CTRT at our institute.

Between January 2008 and July 2015, 201 patients with histologically proven, non-metastatic LA-NPC treated with taxane-based ICT followed by CTRT at our institute and maintained in a prospective database were included in the analysis. The initial evaluation included a complete physical examination, nasopharyngoscopy, a biopsy from the primary or lymph node, contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) of the head and neck region. Eighty per cent of patients had a baseline FDG positron emission tomography-computed tomography (PET-CT) scan, which constituted the metastatic work-up. World Health Organization criteria were used for histological grading of the tumours and patients were staged as per the 2007 American Joint Committee on Cancer staging system.

Relevant patient and tumour-related characteristics are enumerated in Table 1. The median age was 42 years (range: 18–73 years) and most (76%) were men. The most common histology was undifferentiated carcinoma and was seen in 94.5% of patients. Most patients were locoregionally advanced at presentation (stage III/IV 83.5%), with 47% having tumour stage T3–T4 primaries and 68% having nodal stage N2–N3.

Treatment Details and Characteristics

All patients received at least two cycles of ICT, which was followed by concurrent CTRT within 4 weeks of the second cycle. Radiotherapy was delivered using an IMRT technique in all patients.

Chemotherapy Details

All patients received taxane-based ICT, which was either a TIP regimen: intravenous paclitaxel 175 mg/m^2 (day 1) + intravenous ifosfamide 1200 mg/m^2 (days 1–5) + intravenous cisplatin 15 mg/m^2 (days 2–6), the ICT protocol between 2008 and 2012, or a TPF regimen: intravenous docetaxel 75 mg/m^2 (day 1) + intravenous cisplatin 75 mg/m^2 (day 1) + intravenous 5-fluorouracil 750 mg/m^2 (days 1–5), the protocol during 2012–2015 with appropriate concomitant medications.

Granulocyte colony stimulating factor prophylaxis was given to all patients on the TPF regimen. Cycles were repeated every 3 weeks for two to three cycles. Younger patients with better reserves were offered the triplet regimen described above. Patients with dihydropyrimidine dehydrogenase deficiency or patients considered not suitable for a three-drug regimen were treated with a two-drug regimen of paclitaxel + carboplatin (during the 2008–2012 period) or docetaxel + cisplatin (during the 2012–2015 period) and the 5-fluorouracil was omitted. The decision to

Table 1
Patient- and tumour-related characteristics

Characteristic		Number	%
Gender	Male	146	72.5
	Female	55	27.5
Age group	<35 years	76	38
	>35 years	125	62
Histology	KSCC	6	3
	NKSCC	5	2.5
	UD	190	94.5
Tumour stage (T)	T1	46	23
	T2	61	30
	T3	38	19
	T4	56	28
Nodal stage (N)	N0	13	7
	N1	53	26
	N2	87	43
	N3	48	24
AJCC 2007 stage group	II	34	17
	III	76	38
	IVA	44	22
	IVB	47	23

AJCC, American Joint Committee on Cancer; KSCC, keratinising squamous cell carcinoma; NKSCC, non-keratinising squamous cell carcinoma; UD, undifferentiated carcinoma.

administer the triplet or the doublet regimen was at the discretion of the treating physician, as was the decision to administer two or three cycles of ICT. However, since the publication of the trial by Sun *et al.* [11] we now offer all patients three cycles of ICT. ICT was followed by radiotherapy delivered concurrently with weekly cisplatin at 30 mg/m^2. The chemotherapy-related toxicities were graded in accordance with Common Terminology Criteria for Adverse Events (version 3.0). The tumour response to induction therapy was evaluated before the start of CTRT by physical examination and MRI scan.

Radiotherapy Details

Radiotherapy planning was carried out on CECT scans of 2.5 mm slice thickness, obtained after immobilisation in a thermoplastic mould. Delineation of the gross tumour volume (GTV) was carried out on these axial CECT images. The GTV included the gross disease in the nasopharynx as well as any grossly positive nodes. MRI and FDG PET-CT information was used whenever available. The clinical target volume (CTV) was delineated as a high-risk CTV region (HR-CTV) and a low-risk CTV region (LR-CTV) depending on the risk of recurrence.

A HR-CTV included all the area (the primary as well as lymph node regions) involved pre-chemotherapy. A HR-CTV was defined as the nasopharyngeal GTV plus a 5 mm margin, the entire nasopharynx, skull base, sphenoid sinus (if involved), parapharyngeal space, medial pterygoid fossae, posterior parts of the nasal cavity, retropharyngeal nodal regions and involved nodal regions (nodal GTV). When there was a gross intracranial extension or when there was infiltration of surrounding neurological structures, in place of a HR-CTV, a CTV-IC was generated with a 2–5 mm margin to the GTV in this region. The GTV below the level of critical neurological structures and involved lymph node regions was contoured as a HR-CTV. This was carried out to respect the tolerance of the neurological structures, balancing the dose needed for optimal tumour control. A LR-CTV was a volume that encompassed the uninvolved lymph node regions. CTVs were not edited from the parotid on the side of the nodal involvement. Corresponding planning target volumes (HR-PTV, PTV-IC and LR-PTV) were then generated from the three CTVs by growing them by 5 mm. There were substantial variations in the daily dose fraction that was used, which ranged from 2 to 2.2 Gy per fraction. Table 2 summarises the various dose prescriptions used.

All patients were treated with seven-to nine-field LA-based IMRT or Tomotherapy-based IMRT with concurrent weekly cisplatin at 30 mg/m^2 weeks 1–7. Treatment verification was carried out weekly or more frequently if necessary using electronic portal imaging device (EPID) or cone beam computed tomography. All patients were reviewed weekly during treatment for weight, acute toxicity and compliance. Radiation-related acute toxicities were scored according to the Radiation Therapy Oncology Group acute toxicity criteria.

Follow-up

The tumour response to CTRT was evaluated by nasopharyngoscopy, physical examination and PET-CT at 8–12 weeks after the completion of CTRT. The tumour response was classified according to the Response Evaluation Criteria in Solid Tumours (version 1.1). Patients were then followed up every 3 months in the first 2 years, every 6 months in the third and fourth years, and yearly thereafter. The following assessments were carried out at each follow-up visit: history and physical examination, nasopharyngoscopy and late radiotherapy toxicity of the skin, subcutaneous tissue and salivary gland using the late radiation morbidity scoring criteria of the Radiation Therapy Oncology Group. PET-CT was carried out annually or in cases of suspected recurrence. A recurrence was then confirmed with a biopsy/fine-needle aspiration cytology (FNAC) whenever feasible.

Treatment Characteristics

Most patients (84%) received two cycles of ICT and 12% received three cycles. After the completion of ICT, a complete response was seen in 20%, a partial response in 72%, stable disease in 8% and none had disease progression. The most common radiotherapy dose prescription was 66 Gy over 30 fractions in 6 weeks (67.5%) delivered as a simultaneous integrated boost. Overall, 95% of patients completed the prescribed radiotherapy dose and 72% of patients received at least six cycles of concurrent cisplatin. Overall compliance to CTRT was 92%. A complete response

Table 2
Departmental protocol of target volume dose

Target volume	Dose protocol 1	Dose protocol 2
HR-CTV (nasopharyngeal primary + adjacent areas at risk for microscopic extension + involved nodal levels)	66 Gy/30 fractions/6 weeks	70 Gy/35 fractions/7 weeks
LR-CTV (uninvolved neck nodal regions)	54 Gy/30 fractions/6 weeks	56 Gy/35 fractions/7 weeks
CTV-IC (intracranial part of gross tumour volume with margins)	63 Gy/30 fractions/6 weeks	63 Gy/35 fractions/7 weeks
HR-PTV (HR-CTV with 5 mm expansion)	66 Gy/30 fractions/6 weeks	70 Gy/35 fractions/7 weeks
LR-PTV (LR-CTV with 5 mm expansion)	54 Gy/30 fractions/6 weeks	56 Gy/35 fractions/7 weeks

CTV-IC, Intracranial clinical target volume; HR-CTV, high-risk clinical target volume; HR-PTV, high-risk planning target volume; LR-CTV, low-risk clinical target volume; LR-PTV, low-risk planning target volume.

after the completion of radiotherapy was seen in 92% of patients. Treatment characteristics are further highlighted in Table 3.

Statistical Analysis

DFS was the primary end point and was calculated from the date of diagnosis until the date of disease progression or death (whichever occurred earlier) or last follow-up. LRFS, distant metastasis-free survival (DMFS) and overall survival were the secondary end points. The DFS, LRFS, DMFS and overall survival curves were computed using the Kaplan–Meier method and the Log-rank test was used to test the difference between groups. A multivariate Cox proportional hazards model was used to test the prognostic factors and hazard ratios were reported with a 95% confidence interval. All statistical analyses were carried out using SPSS, version 21.0.0 (SPSS Inc., Chicago, IL, USA).

Results

Patterns of Failure

In total, 60 patients experienced failures (Table 4) and distant metastases were the most common (n = 31, 52%). Among distant failures, bone was the most common site (70%), followed by liver and lung. Isolated local and nodal failure was seen in only eight and 13 patients, respectively, and a combination was seen in eight patients. Two patients experienced second primary malignancies, one patient developed cancer in the hypopharynx and the other developed an ovarian neoplasm.

Twenty-nine patients were considered for salvage treatments. However, at the last follow-up, only 13 out of 60 patients (21.7%) were alive and disease-free, five of whom were salvaged after nodal failures, six from solitary distant failures and both the patients with second primary malignancy remain controlled.

Disease-free Survival, Locoregional Relapse-free Survival, Overall Survival and Distant Metastasis-free Survival

After a median follow-up of 37 months (range: 7–110 months), 25 patients had died and 176 patients were alive (23 patients were alive with disease). Among the 25 patients who had died, 23 succumbed to cancer; the other two deaths were non-cancer: one each due to a cardiac cause and a domestic accident. The 3-year DFS, LRFS, DMFS and overall survival of the entire cohort was 72, 85, 83 and 87.4%, respectively (Figure 1).

Table 3
Treatment-related characteristics

Characteristic			No.	%
Induction chemotherapy regimen	TIP		82	41
	PC		39	19
	DCF		67	34
	DC		13	6
Radiotherapy dose prescription and compliance	66 Gy/30 fractions	Complete	136	67.5
		Incomplete	3	1.5
	70 Gy/35 fractions	Complete	54	27
		Incomplete	8	4

DC, docetaxel + cisplatin; DCF, docetaxel + cisplatin + 5-fluorouracil; PC, paclitaxel + carboplatin; TIP, paclitaxel + ifosfamide + cisplatin.

Table 4
Patterns of failure for the entire cohort

Failure pattern	Stage grouping		Frequency (%)	Last follow-up status
	II/III	IV		
No failures	89	52	141 (70)	ANED-140, DdO-1
Persistent primary	1	3	4 (2)	AwD-1, DdD-3
Persistent node	1	1	2 (1)	ANED-2
Persistent primary + node	2	2	4 (2)	AwD-2, DdD-2
Primary recurrence	2	2	4 (2)	ANED-1, AwD-3
Nodal recurrence	5	4	9 (4.5)	ANED-2, AwD-4, DdD-2, DdO-1
Primary and nodal recurrence	3	1	4 (2)	AwD-3, DdD-1
Distant metastases	7	20	27 (13.5)	ANED-6, AwD-9, DdD-12
Primary/nodal recurrence with distant metastases	0	4	4 (2)	AwD-1, DdD-3
Second primary	0	2	2 (1)	ANED-2
Total	110	91	201	ANED-153, AwD-23, DdD-23, DdO-2

ANED, alive with no evidence of disease; AwD, alive with disease; DdD, died due to disease; DdO, died due to other causes.

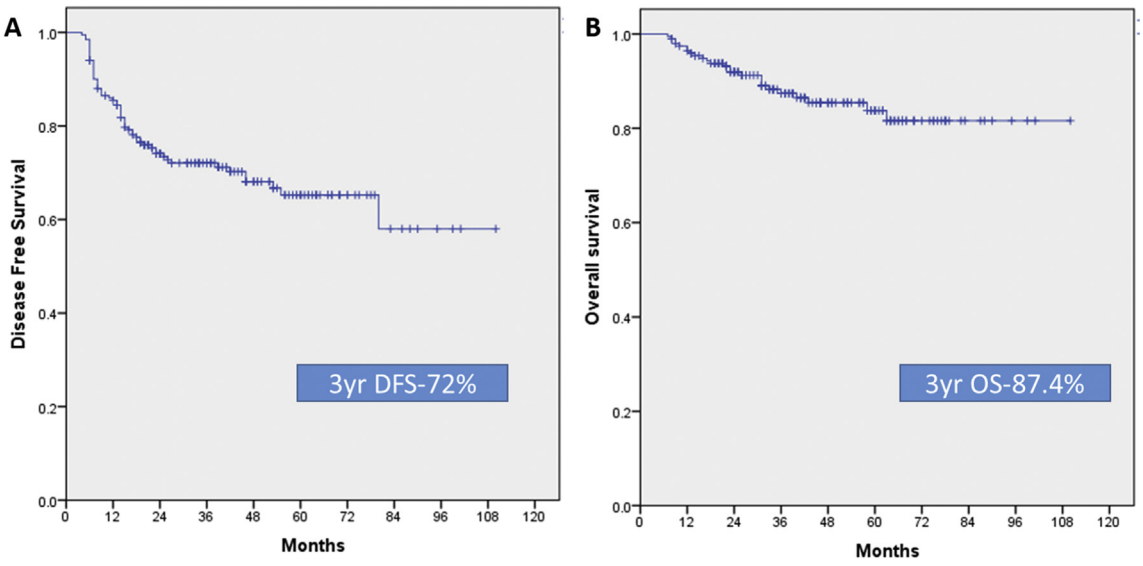

Fig 1. Kaplan–Meier curves for disease-free survival (A) and overall survival (B).

Table 5
Prognostic factors on univariate analysis

Prognostic factor	Subtype (*n*)	3-year DFS % (*P* value)	3-year LRFS % (*P* value)	3-year DMFS % (*P* value)	3-year OS % (*P* value)
Age	<35 years (76)	74	85	87	86
	>35 years (125)	70 (0.26)	74 (0.39)	82 (0.84)	88 (0.87)
Gender	Male (146)	71	85	82	88
	Female (55)	72 (0.95)	83 (0.87)	86 (0.61)	86 (0.84)
Histology	Undifferentiated (190)	74	87	85	89
	Rest (11)	27 (0.00)	48 (0.00)	46 (0.029)	46 (0.004)
Tumour stage	T1–T3 (145)	76	85	88	91
	T4 (56)	60 (0.027)	82 (0.617)	70 (0.006)	78 (0.025)
Nodal stage	N0–N1 (66)	81	85	92	92
	N2–N3 (135)	67 (0.031)	83 (0.367)	79 (0.010)	85 (0.040)
Stage group	II/III (110)	81	87	93	92
	IVA/B (91)	60 (0.000)	81 (0.131)	71 (0.000)	81 (0.064)
ICT response	CR (54)	70	92	80	87
	<CR (147)	70 (0.418)	83 (0.134)	83 (0.794)	86 (0.354)
Post-CTRT response	CR (184)	76	91	83	90
	<CR (17)	18 (0.000)	18 (0.000)	84 (0.483)	51 (0.001)

CR, complete response; CTRT, chemoradiotherapy; DFS, disease-free survival; DMFS, distant metastasis-free survival; ICT, induction chemotherapy; LRFS, locoregional relapse-free survival; OS, overall survival.

On univariate analysis (Table 5), histology was a significant predictor of all the survival outcomes (DFS, LRFS, DMFS and overall survival), with histologies other than undifferentiated outcome predicting a worse outcome. T-/N-stage was a significant predictor of DFS, DMFS and overall survival, with no significant impact on LRFS, whereas a complete response to CTRT predicted for a better DFS, LRFS and overall survival. Age, gender, ethnicity and response to ICT did not affect any of the outcomes significantly. Radiotherapy dose was not included in the univariate analysis, as only a very small percentage of patients did not complete the prescribed dose.

A multivariate analysis was carried out using the Cox proportional hazards model for each of the outcomes and is depicted in Table 6. Histology retained its prognostic significance for DFS, LRFS and overall survival, predicting a worse outcome for histologies other than undifferentiated carcinoma. Although the N-stage was an independent predictor of DFS, DMFS and overall survival, T-stage was not a significant predictor for any of the outcomes. A partial response to CTRT was a predictor of worse LRFS and DFS.

Toxicity

During ICT, 55 (27.5%) patients developed grade 3 or worse haematological toxicities; grade 3 or 4 neutropenia occurred in 50 (25%) patients, followed by leukopenia (48; 24%), thrombocytopenia (10; 5%) and anaemia (eight; 4%).

Table 6
Multivariate analysis

Variables	DFS			LRFS			DMFS			OS		
	P	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI
Histology: rest	0.001	3.42	1.65–7.11	0.02	4.34	1.73–10.8	0.052	2.86	0.99–8.27	0.006	4.89	1.59–15.1
T stage: T4	0.76	1.08	0.64–1.82	–	–	–	0.275	1.49	0.72–3.06	0.243	1.63	0.71–3.72
N Stage: N2–3	0.019	2.05	1.13–3.74	–	–	–	0.015	3.68	1.3–10.54	0.035	3.18	1.08–9.37
Post-CTRT: PR	0.000	7.60	4.05–14.2	0.00	21.0	9.9–44.3	–	–	–	0.001	4.82	1.88–12.3

CI, confidence interval; CTRT, chemoradiotherapy; DFS, disease-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, locoregional relapse-free survival; OS, overall survival; PR, partial response.

Grade 3 or worse non-haematological toxicities, which included stomatitis, nausea, vomiting and electrolyte disturbances, were seen in 80 (40%) patients.

The acute toxicities during CTRT were primarily related to skin and mucosa. Grade 2 or worse acute skin and mucosal toxicity were seen in 77 and 89% of patients during CTRT, of which grade 3 constituted 10 and 4%, respectively. Grade 3 or 4 haematological toxicities were seen in 14% of patients (leukopenia [13.5%], neutropenia [11.5%], thrombocytopenia [1%] and anaemia [2.5%]) during CTRT. Ten (5%) patients required hospital admissions for supportive care due to acute toxicities and in 16 (8%) patients the treatment needed to be interrupted; however, only 10 (5%) patients could not complete the intended dose of radiotherapy.

Late toxicities that were recorded were grade 2 or worse subcutaneous fibrosis seen in 19% of patients, xerostomia seen in 24% of patients and hearing loss in 6% of patients at the last follow-up. Thirty-nine per cent of patients developed hypothyroidism at the last follow-up and required thyroxine supplementation. There were no instances of neurological or vascular sequelae.

Discussion

Concurrent CTRT with or without ACT is considered to be the standard of care for LA-NPC, with an excellent locoregional control, reaching 90% at 3 years across various IMRT series. However, a significant proportion of patients fail at distant sites after CTRT, necessitating the intensification of systemic treatment with additional chemotherapy.

However, the role of ACT is uncertain, with the initial individual patient data meta-analysis by Baujat *et al.* [6] concluding that the highest benefit resulted from the concurrently administered chemotherapy. The update of this meta-analysis by Blanchard *et al.* [10], which examined the effect of concomitant chemotherapy with and without ACT as distinct groups, failed to define the exact benefit with ACT. Furthermore, the randomised controlled trial [14] evaluating the benefit of ACT to CTRT also failed to show a significant benefit over CTRT. This apparent lack of significant benefit with ACT is probably due to poor compliance to ACT after CTRT. Hence, ICT was revisited as the method for systemic intensification. With excellent compliance and an acceptable toxicity profile in various phase II studies, ICT was then tested across various randomised control trials. Two randomised phase II trials by Fountzilas *et al.* [15] and Hui *et al.* [16] comparing ICT followed by CTRT versus CTRT alone showed promising results with ICT, the trial by Hui *et al.* [16] showing an overall survival benefit with only 65 patients. However, this overall survival benefit was not reproduced in an initial phase III trial by Tan *et al.* [17], which showed no difference in any of the outcomes with ICT. However, this study assumed a 15% difference in overall survival with the addition of ICT and the small sample size was clearly underpowered to detect this small difference.

Recently, a larger phase III trial of ICT plus CTRT versus CTRT alone in LA-NPC by Sun *et al.* [11] showed a significant benefit with ICT in distant failure-free survival, failure-free survival and overall survival. The 3-year failure-free survival, locoregional failure-free survival, distant failure-free survival and overall survival in the ICT plus CTRT arm was 80, 92, 90 and 92%, respectively, compared with 72, 89, 83 and 86%, respectively, in the CTRT arm. The 3-year DFS, LRFS, DMFS and overall survival in our study was 71.3, 85, 83 and 87.4%, respectively, similar to the CTRT-alone arm in the abovementioned study. The distant metastases rate in our study was 15%, intermediate between the CTRT arm (18%) and the ICT + CTRT arm (11%) of Sun *et al.* This difference in results may be explained by the inclusion of keratinising squamous cell carcinoma/non-keratinising squamous cell carcinoma (KSCC/NKSCC) histological variants, a larger proportion of higher N-stages, fewer ICT cycles and a smaller cumulative dose of concurrent cisplatin in our cohort of patients.

Multivariate analysis showed that histology was the most important predictor of locoregional control and thus influenced DFS and overall survival. Although KSCC/NKSCC constituted only a small proportion of our patients ($n = 11$), they had significantly poorer outcomes, with nine failures and four distant metastases (Table 5). If these patients were excluded to match the inclusion criteria in the trial of Sun *et al.* [11], our results would be a little closer to those of the ICT arm of the Sun *et al.* trial, as seen in Table 5. The N-stage is considered to be the most important determinant of DMFS, DFS and overall survival in NPC, which is also evident in our study, as well as in the trial by Sun *et al.* [11]. A larger proportion of patients with higher N-stages would mean a higher distant metastases rate. Sixty-seven per cent of patients in our cohort had N2–3 stages and 24% had N3 disease compared with 60% with N2–3 and 16% with N3 disease in the study by Sun *et al.* [11]. This could partly

explain the higher distant metastases rate in our study. Although 88% of patients in the ICT arm of Sun *et al.* received three cycles of ICT, only 12% of patients received three cycles of ICT in our study. Similarly, although 88% of patients in the randomised controlled trial received a cumulative cisplatin dose (CCD) $\geq$200 mg/m^2, only 25% of patients in our study achieved such cumulative doses. Although higher doses of individual drugs were used in our ICT regimen, which is considered standard for the TPF regimen, when compared with the regimen of Sun *et al.*, it is unlikely that this could have compensated for one less cycle of ICT and a lower CCD, in the presence of such advanced nodal disease, thus resulting in the observed deviation from the results of the ICT arm of Sun *et al.* [11].

Although our results seem similar to the chemoradiation arm, adjustment for N-stages and exclusion of KSCC/NKSCC histology to match the Sun *et al.* trial would probably drive our results much closer to the ICT arm of the randomised controlled trial. Given the results, we could possibly surmise that if all patients had received three cycles of ICT, the results might have been equivalent to those reported by Sun *et al.*, considering the higher doses of chemotherapy drugs used by us. Our study thus provides a reasonable estimate of results for patients who may not tolerate three cycles of an intense ICT regimen, especially if given at standard doses, as in our study.

Although one may question our CTRT regimen (a weekly cisplatin dose of 30 mg/m^2) and describe it as non-standard, this dose is actually not uncommon and has been described in various retrospective studies [18–21] and phase III trials [22–25] of head and neck cancer and NPC. Although a CCD of 200 mg/m^2 was not reached with our CTRT regimen, higher doses of cisplatin (75 mg/m^2) used in our ICT regimen compared with the Sun *et al.* ICT regimen (60 mg/m^2) may result in a similar overall CCD, especially in patients receiving three cycles of ICT. Recently, studies [26,27] have questioned the previously defined CCD threshold of 200 mg/m^2 and described similar survival even with a CCD $<$ 200 mg/m^2, especially in patients receiving additional ICT [27]. In a propensity-matched study of 583 patients of LA-NPC, Lv *et al.* [27] concluded that the causal relationship between 200 mg/m^2 CCD and improved survival was not defined; 160 mg/m^2 CCD might be enough in patients receiving three cycles of ICT. A few other studies [28,29] have even questioned the value of concurrent cisplatin in patients receiving IMRT for LA-NPC. In a retrospective study [29] of 214 patients with LA-NPC with low nodal burden there was no difference in survival between CTRT and ICT followed by radiotherapy alone.

Acute skin and mucosal toxicity rates in the current study seem to be comparable with our previously published data of IMRT in head and neck cancer [0]. About 70–80% of patients do develop grade 2 toxicities; however, grade 3 toxicities are seen in only 5–10% of patients and seem acceptable. Rates of grade 2 or worse subcutaneous fibrosis and xerostomia are also comparable [0] and thus ICT does not seem to increase the rates of toxicities from IMRT.

The strength of our study is that it provides the lower limit of benefit with ICT, assuming that a reasonable proportion of patients would only tolerate two cycles of ICT when given at standard doses. It also shows the outcomes with ICT in a non-endemic cohort, which may include a certain percentage of histological variants other than the undifferentiated variants. ICT also provides certain logistic benefits, such as a reduction in the number of re-planning sessions and improvement in dose conformity [1]. Therefore, it is ideal for our setting with advanced stages at presentation and long waiting times for radiotherapy appointments.

For the future, we will consider intensifying our systemic treatments, starting with increasing the number of ICT cycles in our patients. Studies to stratify patients into risk groups that may benefit the most with treatment intensification are ongoing at our institute.

Conclusion

ICT followed by concurrent CTRT in the IMRT era provides excellent locoregional control, distant control and overall survival rates in patients with LA-NPC. However, distant failure continues to be a problem and may require further systemic intensification.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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